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Original Contributions

Spectrum of neuroendocrine carcinomas of the uterine cervix, including histopathologic features, terminology, immunohistochemical profile, and clinical outcomes in a series of 50 cases from a single institution in India

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ABSTRACT

Neuroendocrine carcinomas of the cervix are uncommon, characterized by a histomorphological spectrum and, mostly, an aggressive clinical course. There are only few substantial studies on such cases documented from our country, where cervical cancer is the second most common cancer affecting women. Herein, we present a spectrum of 50 cervical neuroendocrine carcinomas, including histopathologic features, terminology, immunohistochemical (IHC) profile, and clinical outcomes, wherever available. Fifty tumors occurred in women, with their age ranging from 23 to 69 years (mean, 48.6 years; median, 46.5 years). Stagewise, among 25 cases, most cases (6, or 24%) presented with stage IB. Average tumor size was 4.7 cm. On histopathologic review, 26 tumors (52%) were classified as small cell carcinoma (SMCA); 14 (28%), as large cell neuroendocrine carcinomas (LCNECs); 4 (8%), as SMCA + LCNECs; and 6, as mixed carcinomas, including 3 tumors (6%) with SMCA and squamous cell carcinoma (SCC), 2 tumors (4%) with LCNEC and adenocarcinoma, and a single tumor (2%) with LCNEC and squamous cell carcinoma. On IHC performed in 41 tumors (82%), 36 tumors (87.8%) were positive for at least a single neuroendocrine marker, and 22 (53.6%) expressed 2 neuroendocrine markers. Synaptophysin was positive in 22 (59.4%) of 37 tumors; chromogranin, in 27 (72.9%) of 37; CD56, in 8 (100%) of 8; and neuron-specific enolase in 7 (87.5%) of 8 tumors. Treatment wise, among 30 patients (60%), 6 (20%) underwent surgery, including Wertheim hysterectomy (5) and simple hysterectomy (1); 8 (26.6%) underwent surgery with adjuvant treatment, and 10 patients (33.3%) were offered chemotherapy and/or radiotherapy. On follow-up (27 patients, or 54%) over 1 to 144 months, 16 patients (59.2%) were alive with disease over median duration of 9 months, and 7 (25.9%) were free of disease over median duration of 26.5 months. There were 5 recorded deaths. Thirteen tumors (48.1%) metastasized, most commonly to liver. In cases with early stage disease and adjuvant treatment, including radiotherapy, LCNEC histology fared well. This study forms the largest documented series on cervical neuroendocrine carcinomas from our country, testifying the current histopathologic classification system. Although SMCAs can be recognized on morphology, LCNECs need to be correctly identified because these can be misdiagnosed in the absence of neuroendocrine markers. Synaptophysin, chromogranin, and CD56 are optimal IHC markers. Small cell carcinomas, pure or mixed, are relatively more aggressive. All these tumors are best treated with multimodal therapy. Early stage disease treated with radical surgery and adjuvant treatment seems to increase survival. Despite aggressive treatment, prognosis is dismal.

1. Introduction

Cervix cancer is the second most common female cancer, annually constituting 16% of cancer cases affecting women registered at our tertiary cancer referral center [1-3]. Neuroendocrine carcinomas of the uterine cervix are uncommon and account for 0.5% to 1% carcinomas of cervix, as per Western literature [4-7]. At our hospital,

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these form 0.6% of diagnosed cervical cancers [3]. Histologically, these tumors are subdivided into carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma (LCNEC), and small cell carcinoma (SMCA), as per recommendations from the College of American Pathologists and National Cancer Institute [4-7]. Although the former 2 subtypes have been uncommonly documented and the latter entity has been the most commonly documented neuroendocrine carcinoma of cervix, LCNEC is another neuroendocrine carcinoma with a histomorphological spectrum and is frequently misdiagnosed [4-10]. Neuroendocrine differentiation in cervix carcinomas is either identified as distinct tumor type or, uncommonly, as a tumor component with other cervical carcinomas, namely, squamous and adenocarcinomas (ADCAs) [10-14]. Within neuroendocrine carcinomas, component of LCNEC can coexist with an SMCA [11,12]. Focal neuroendocrine differentiation is also noted, more commonly in ADCAs [15].

Although focal neuroendocrine differentiation in other carcinomas is not related to prognosis, neuroendocrine carcinomas, especially LCNEC and SMCA, either as "pure" of mixed tumors are associated with an aggressive clinical course and therefore treated with multimodal approach, including surgery with adjuvant chemotherapy (CT) and or radiotherapy (RT), depending upon clinical and pathological staging [6-10,15,16]. Most studies on cervical neuroendocrine carcinomas have been from the West [4-8,10,11]. There have been limited studies with substantial number of cases, documented from our continent, where cervical carcinoma forms a major cancer burden [9,13,17,18].

Herein, we present clinicopathologic spectrum of 50 neuroendocrine carcinomas of the uterine cervix, including treatment and clinical outcomes, wherever possible.

2. Materials and methods

The medical records and case files of the Tata Memorial Hospital (TMH) were searched for cervix carcinomas diagnosed as SMCA, LCNEC, carcinoid, poorly differentiated carcinoma with neuroendocrine differentiation, ADCA or squamous cell carcinoma (SCC) with neuroendocrine differentiation, or neuroendocrine carcinoma over a period of 7 years.

A total of 50 cases were included in the study after review by BR (pathologist from Gynaec Oncology working group) with BP, as per current diagnostic criteria [4]. Clinical details were procured from case files and/or electronic medical records across hospital information system.

The diagnostic material was in form of biopsy specimens (15, or 30%); "in-house" resection specimens (7, or 14%); paraffin blocks, either from biopsies or excisions (22, or 44%); and stained slides (6, or 12%). The latter 2 types of samples constituted as referral material. One case was accompanied with imprint cytologic smears stained with Papanicolaou stain. The resection specimens were Wertheim hysterectomy (5) and total abdominal hysterectomy with bilateral salpingo-oophorectomy and lymph nodes (2). Clinical staging was done as per International Federation of Gynaecology and Obstetrics system for carcinoma cervix.

Conventional hematoxylin and eosin–stained microsections were available in cases. Immunohistochemical (IHC) results were available in 41 tumors (82%).

2.1. Immunohistochemical analysis

Immunohistochemistry was performed by immunoperxoidase method using MAC H2 Universal HRP-Polymer detection kit (Biocare, Pike Lane Concord, CA) including 3′-3′-diaminobenzidine tetrahydrochloride as the chromogen. Staining for neuroendocrine markers was considered positive if it was noted in more than 10% of tumor cells. For other markers, staining was graded as 0, 1+ (<10% tumor cells), 2+ (10%-50%), or 3+ (>50%). Appropriate positive and negative controls were included. The details of the various antibody markers are enlisted in Table 1.

3. Results

Fifty tumors occurred in women, with their age ranging from 23 to 69 years (mean, 48.6 years; median, 46.5 years). Bleeding (15), vaginal discharge (10), and pain (8) were the symptoms recorded in 23 patients (46%). Details regarding initial tumor (T) stage were available in 25 cases (50%). Of these, most patients (6, or 24%) initially presented with stage I (all with stage IB), followed by 5 (20%) each, who presented with stage IIB and IIIB, respectively; 4 (16%) with stage IV; 3 patients (12%) who presented with stage IIA; and the remaining 2 (8%) with stage IIIA disease. In addition, 3 patients, previously operated elsewhere, presented at our center with stage IV disease. T size in 27 tumors (54%) varied from 1 to 7.3 cm in maximum dimension (mean, 4.7 cm).

On review, 26 tumors (52%) were classified as SMCAs; 14 (28%), as LCNECs; 4 (8%), as SMCA + LCNECs; and 6 tumors, as mixed carcinomas, including 3 tumors (6%) that displayed discrete areas of SMCA as well as those of SCC, 2 tumors (4%) that revealed areas of LCNEC and ADCA, and a single tumor (2%) that showed components of LCNEC and SCC.

Table 1
List of various antibody markers in the present study

Sr no.	Antibody marker	Clonality, clone	Dilution	Antigen retrieval	Manufacturer
1	Synaptophysin	Polyclonal	1:100	Heat (Tris-EDTA) Pascal	Thermo Scientific, PA, USA
2	Chromogranin	Polyclonal	1:250	Heat (Tris-EDTA) Pascal	Dako, Glostrup, Denmark
3	CD56 (N-CAM)	Monoclonal, Bc56C04	1:50	Heat (Tris-EDTA) Pascal	Dako
4	NSE	Monoclonal, BsNcHI4	1:100	Enzymatic, pepsin	Dako
5	EMA	Monoclonal, E 29	1:200	Heat (Tris-EDTA) Pascal	Dako, Produkionsveg, Glostrup, Denmark
6	CK	Monoclonal, MNF116	1:200	Heat (Tris-EDTA) Pascal	Dako
7	Vimentin	Monoclonal, V9	1:400	Heat (Tris-EDTA) Microwave	Dako
8	P63	Monoclonal	1:200	Heat (Tris-EDTA) Pascal	Dako
9	CK7	Monoclonal, OV-TL-12/30	1:100	Heat (Tris-EDTA) Microwave	Dako
10	CK20	Monoclonal, Ks 20.8	1:50	Heat (Tris-EDTA) microwave	Dako
11	TTF-1	Monoclonal, 8F7G3/1	1:100	Heat (sodium citrate) microwave	Dako
12	CEA	Polyclonal	1:600	Enzymatic (pepsin)	Dako
13	S100-P	Polyclonal	1:300	Heat (Tris-EDTA) Pascal	Dako
14	MIC2/CD99	Monoclonal, 12E7	1:50	Heat (Tris-EDTA) Pascal	Dako

CK indicates cytokeratin; N-CAM, Neural cell adhesion molecule.